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# Primary Carcinoma of the Liver in Alberta

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**A survey was made to determine the incidence and to elucidate the manifestations of primary carcinoma of the liver in Alberta. The findings were compared with other reported series. Ninety-six cases were identified: 69 hepatomas, 25 cholangiomas and two cholangiohepatomas. Seventy-four of the patients were male and 22 were female, a male preponderance of greater than 3:1. Ages ranged from 7 days to 92 years, but the majority of the patients (58%) were in the seventh and eighth decades. The incidence of associated cirrhosis (38.5%) was lower than that noted in most series.**

**Hepatomegaly, abdominal pain, weight loss and ascites were the outstanding clinical features. Gastrointestinal hemorrhage was frequent and second only to hepatic failure as the immediate cause of death. An abdominal mass and pleural effusion occurred in higher frequency than that cited in the literature. Associated disorders included peptic ulceration and cholelithiasis.**

**Surgical biopsy was superior to needle biopsy in establishing the diagnosis. Laboratory tests and routine radiographs may be of diagnostic aid.**

**On a procéde à un relevé pour établir la fréquénce et pour étudier les manifestations du cancer primaire du foie dans la province d'Alberta. Les résultats en ont été comparés à ceux d'autres études publiées. On a pu identifier 96 cas: 69 hépatomes, 25 cholangiomes et deux cas de cholangiohépatomes. On comptait 74 malades de sexe masculin et 22 du sexe féminin, soit une prépondérance de 3 ou 4 contre 1 pour les sujets de sexe masculin. L'âge variait de 7 jours à 92 ans, mais la majorité des malades (58%) étaient âgés de 70 à 80 ans. La fréquence de la cirrhose (38.5%) était plus basse que celle qui avait été notée dans la plupart des autres séries.**

**Parmi les caractéristiques cliniques importantes, figuraient hépatomégalie, douleur abdominale, perte de poids et ascite. L'hémorragie gastro-intestinale était fréquente et suivait de prés l'insuffisance hépatique comme cause immédiate de la mort. Une masse abdominale et un épanchement pleural sont survenus plus souvent dans cette série que dans d'autres séries citées dans la documentation. Parmi les troubles associés figuraient des cas d'ulcères gastro-duodénaux et de cholélithiases.**

**La biopsie chirurgicale s'est révélée supérieure à la biopsie par aiguille pour établir le diagnostic. Les épreuves de laboratoire et les radiographies peuvent constituer des aides diagnostiques.**

CURRENT interest in primary liver cancer is probably due to recent reports of its early diagnosis and, in a few cases, successful surgical eradication. Many of the published series deal with a single locale or hospital population—often with a marked ethnic basis which influences the results; for example, Strong, Pitts and McPhee[1] in 1949 reported a series of 55 cases from Vancouver General Hospital which included 35 Chinese. A comparable racial distribution was reported by Wilbur, Wood and Willett[2] in 1944 from San Francisco. Both cities have a relatively high Chinese population. The heterogenous nature of the population of the western provinces and states reduces such ethnic bias to a minimum.

The present survey included all available cases of primary cancer of the liver in Alberta for the 16-year period 1949-1965. Cases were drawn from the 11 hospitals in the province with pathology departments, from the three Provincial Cancer Diagnostic Clinics and from the Provincial Laboratory of Public Health. The sources of the 96 cases were as follows: 67 cases were from the Edmonton area (population: 349,233), 21 from the Calgary area (population: 290,000) and eight from the Lethbridge district (population: 35,454). All case histories were reviewed by the authors. The diagnosis was in all instances confirmed by autopsy (the rate of primary hepatic carcinoma at the Uni-

TABLE I.—PRIMARY HEPATIC CARCINOMA—96 CASES

| | | *Sex incidence* | |
|---|---|---|---|
| | | *Males* | *Females* |
| Hepatoma | 69 ( 72%) | 55 | 14 |
| Cholangioma | 25 ( 26%) | 17 | 8 |
| Cholangiohepatoma | 2 ( 2%) | 2 | 0 |
| Total | 96 (100%) | 74 (77%) | 22 (23%) |

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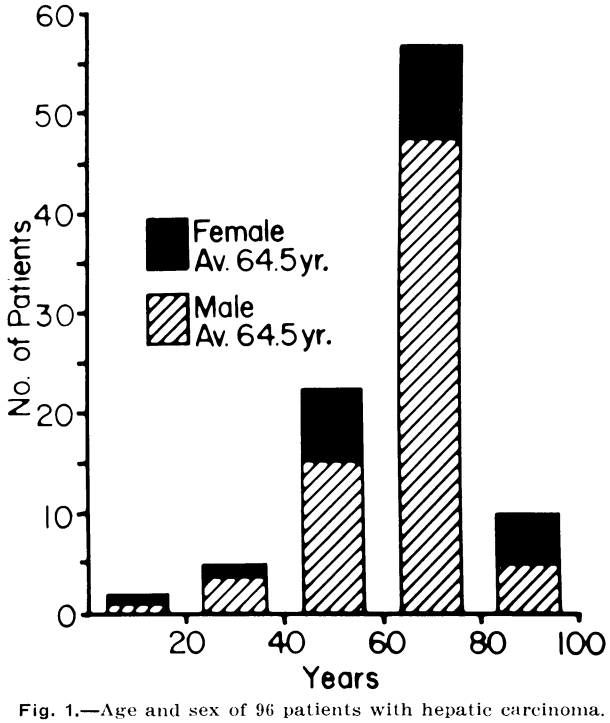


Fig. 1.—Age and sex of 96 patients with hepatic carcinoma.

versity of Alberta Hospital was 0.29%), laparotomy or needle biopsy.

In this series only hepatic carcinomas are considered. As is shown in Table I, there were 69 hepatomas, 25 cholangiomas and two cholangiohepatomas. Seventy-four of the patients were male and 22 were female. The series included 87 Caucasians, seven Chinese and two North American Indians.

There was a wide age range, from 7 days to 92 years (Fig. 1); the week-old infant had a congenital hepatoma. The average age on admission to hospital for both sexes was 64.5 years, a little older than in most series.[3-6] Edmondson and Steiner[7] found a lower average age in males than in females, in accordance with the higher frequency of the disease in males. This was not observed in the present survey. The usual male-to-female preponderance of 6:1 cited in the literature[8, 9, 17] was not observed. There were 77% males and 23% females, a ratio greater than 3:1.

The etiology of primary liver cancer has long been a matter of interest. The literature abounds with data correlating cirrhosis and hepatoma,[1, 4, 5, 7, 11, 15] and, more recently, viral hepatitis complicated by postnecrotic cirrhosis has been implicated.[10, 19-21] The most frequent clinical picture is said to be that of a hepatoma complicating the course of cirrhosis, usually in an alcoholic patient. Edmondson and Steiner[7] in 1954 reported that in their series cirrhosis was present in 23% of those with cholangiomas and in 89% of those with hepatomas. In 1963 Elkington, McBrien and Spencer[11] reported that 91% of the hepatomas and 54% of the cholangiomas occurred in cirrhotic patients. In contrast, in the present series, only

TABLE II.—ANALYSIS OF 37 CASES OF CIRRHOSIS AMONG 96 PRIMARY CARCINOMAS OF THE LIVER

| *Carcinoma* | *Total* | *Cirrhosis* *Portal* | *Biliary* | *Per cent* |
|---|---|---|---|---|
| Hepatoma | | | | |
| Males | 55 | 25 | 0 | |
| Females | 14 | 4 | 0 | |
| | 69 | 29 | 0 | 42 |
| Cholangioma | | | | |
| Males | 17 | 4 | 2 | |
| Females | 8 | 1 | 1 | |
| | 25 | 5 | 3 | 32 |
| Cholangiohepatoma | | | | |
| Males | 2 | 0 | 0 | |
| Females | 0 | 0 | 0 | |
| | 2 | 0 | 0 | 0 |
| Total | 96 | 34 | 3 | 38.5 |

42% of hepatomas and 32% of cholangiomas were associated with cirrhosis (Table II). The association was slightly higher in males.

Only 10 patients admitted to being chronic alcoholics; seven of these had cirrhosis at autopsy. This figure is probably unrealistic and errs on the conservative side.

The diagnoses in the present series were made by needle biopsy in five cases, laparotomy biopsy in 20 and necropsy in 72. Of the 72 who came to necropsy, the diagnosis had been established during life in 18: two by needle biopsy and 16 at laparotomy. Thirteen of the 72 had biopsies that failed to identify the primary tumour. Of these, nine were needle biopsies and four were laparotomy biopsies; the erroneous diagnoses in these cases were metastatic carcinoma, cirrhosis and hemochromatosis.

TABLE III.—METASTASES IN 72 PRIMARY CARCINOMAS OF THE LIVER

| | *Number* | *Metastases* | *Per cent* |
|---|---|---|---|
| Hepatoma | 48 | 25 | 52 |
| Cholangioma | 22 | 11 | 50 |
| Cholangiohepatoma | 2 | 2 | 100 |
| Total | 72 | 38 | 53 |

Extrahepatic spread was present in 38 cases, 53% of the 72 cases that came to autopsy (Table III). The presence of distant metastases varied according to tumour type: in 52% of the hepatomas, 50% of the cholangiomas and 100% of the mixed tumours there was evidence of metastatic spread. The sites of metastases in order of frequency (Table IV) were (a) lymph nodes—most often in regional and para-aortic nodes; (b) lungs, (c) adrenals and (d) omentum. Less common sites included the peritoneum, spleen and gallbladder. In addition to vessels which were the site of malignant thrombosis (Table IV), thrombosis occurred without evidence of tumour invasion in the inferior vena cava and portal veins in two cases each and in the hepatic veins in one

TABLE IV.—SITES OF METASTASES—72 CASES

| *Site* | *No.* | *Site* | *No.* |
|---|---|---|---|
| Lymph node involvement | 22 | Spleen | 3 |
| Intra-abdominal | 16 | Gallbladder | 3 |
| Extra-abdominal | 11 | Lumbar vertebrae | 2 |
| Lungs | 20 | Pleura | 2 |
| Right only | 5 | Stomach | 2 |
| Left only | 2 | Diaphragm | 2 |
| Both | 13 | Pancreas | 2 |
| Adrenals | 4 | Inferior vena cava | 2 |
| Omentum | 4 | Portal veins | 2 |
| Peritoneum | 3 | Pulmonary arteries | 2 |

case. Metastatic involvement of the right ovary, sigmoid colon, falciform ligament, mesentery, heart and hepatic veins was found in one patient each. Metastases to the head were conspicuous by their absence. As noted in Table V, the presence or absence of cirrhosis did not significantly influence the frequency of metastatic dissemination.

TABLE V.—ASSOCIATION OF METASTASES AND CIRRHOSIS IN 72 PRIMARY LIVER CARCINOMAS

| | *Total* | *Metastases* | *Per cent* |
|---|---|---|---|
| Cirrhosis | | | |
| Present | 28 | 13 | 46 |
| Absent | 44 | 25 | 57 |
| Total | 72 | 38 | |

Six patients had pancreatic lesions which included acute and chronic pancreatitis, pancreatic cysts, and fat necrosis. Two patients had splenic infarcts.

Associated disorders included peptic ulceration in 15 patients (13 duodenal and two gastric ulcers), diabetes in seven (three idiopathic and four due to hemochromatosis), and chronic cholecystitis with associated cholelithiasis in 22.

In spite of occasional bizzare presentations, the symptoms and signs of primary hepatic malignancy are primarily abdominal in nature. Tables VI and VII summarize the presenting clinical features in 96 cases. Abdominal pain was the most common complaint. Most frequently the primary site was the right upper quadrant, followed closely by

TABLE VI.—SYMPTOMS OF PRIMARY CARCINOMA OF LIVER IN 96 CASES

| | *No.* | *Per cent* |
|---|---|---|
| Pain: RUQ | 34 | 35 |
| Epigastric | 24 | 25 |
| Back | 15 | 16 |
| Chest | 11 | 11 |
| Weight loss | 54 | 56 |
| Abdominal distension | 44 | 46 |
| Anorexia | 44 | 46 |
| Weakness and fatigue | 43 | 45 |
| Dyspnea | 30 | 31 |
| Dyspepsia | 30 | 31 |
| Vomiting | 28 | 29 |
| Abdominal mass | 27 | 28 |
| Diarrhea | 19 | 20 |
| Constipation | 13 | 14 |

TABLE VII.—SIGNS OF PRIMARY CARCINOMA OF LIVER IN 96 CASES

| | *No.* | *Per cent* |
|---|---|---|
| Hepatomegaly | 82 | 85 |
| Ascites | 49 | 51 |
| Icterus | 37 | 39 |
| Peripheral edema | 32 | 33 |
| Gastrointestinal hemorrhage | 26 | 27 |
| Pleural effusion | 21 | 22 |
| Superficial veins | 19 | 20 |

the epigastrium. Back pain, usually between the scapulae and less frequently in the lumbar region, was present in 15 patients, and in all but three instances this was preceded by or associated with abdominal pain. Eleven had chest pain. This was a presenting complaint in only one patient and it was associated with hemoptysis.

Weight loss was the next most common symptom, occurring in 54 patients despite the concomitant development of ascites and/or peripheral edema in 30 of these. Abdominal distension caused by an enlarged liver or ascites, anorexia, weakness and fatigue were of equal incidence. Dyspnea was attributed to ascites, pulmonary metastases and terminal pneumonia. Dyspepsia, nausea and vomiting were frequent. Twenty-seven patients complained of an abdominal mass. Diarrhea and constipation were not infrequent, and these were alternating symptoms in four patients.

Hepatomegaly was the outstanding physical sign, occurring in 82 patients. The liver was palpably nodular in 57 and tender in 31. Ascites, jaundice and peripheral edema were frequent.

Gastrointestinal hemorrhage occurred in 26 patients. It took the form of hematemesis in 19, profuse rectal bleeding in three and melena in four. Fourteen of the 19 patients with hematemesis died of massive hemorrhage: eight from ruptured esophageal varices, one from a chronic duodenal ulcer and one from acute superficial gastric ulcers. Three of the 26 patients exsanguinated terminally from profuse rectal bleeding. Two of these came to necropsy: one had esophageal and rectal varices; the other, portal cirrhosis with a low prothrombin time. The third patient was cirrhotic and had clinical evidence of portal hypertension (splenomegaly and ascites). Four patients had melena only; three of these developed hepatic failure which was attributed to the blood loss. The fourth had a primary adenocarcinoma of the stomach as well as a cholangioma; the former was undoubtedly the source of the melena.

Other bleeding complications included hemoptysis in three patients and epistaxis in two.

Of the 19 patients with dilated superficial abdominal and thoracic veins, 12 were known cirrhotics and one had a malignant thrombosis of the inferior vena cava.

Splenomegaly was an autopsy finding in 12 patients, most frequently in those with hepatomas, and in all but one case there was associated cir-

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TABLE VIII.—LABORATORY DATA

| *Determinations* | *No. patients studied* | *Per cent abnormal* |
|---|---|---|
| Hemoglobin: (♀ < 11 g.) | 17 | 29 |
| (♂ < 12 g.) | 61 | 43 |
| Neutrophilia (absolute) | 72 | 46 |
| ESR (♀ > 10 mm./hr.) | | |
| (♂ > 15 mm./hr.) | 67 | 88 |
| Proteinuria | 71 | 70 |
| Bilirubin | 46 | 76 |
| Thymol turbidity | 24 | 38 |
| CCF | 44 | 57 |
| Prothrombin time (<70%) | 44 | 36 |
| SGOT (>40 units) | 22 | 82 |
| Alkaline phosphatase | 40 | 78 |
| BSP | 24 | 46 |
| Serum albumin (<3.6 g.%) | 52 | 75 |
| Serum globulin (>3.6 g.%) | 52 | 42 |
| Reversed A/G ratio | 52 | 54 |

rhosis. It was recorded as a physical sign in only two of these patients. The spleen was palpable in two patients who did not come to necropsy.

Twenty-one had a pleural effusion; it was bilateral in 12 and involved the left side in five and the right side in four.

Results of laboratory studies are shown in Table VIII. In two patients the anemia was of the macrocytic type. Four males with hepatomas had hemoglobin values exceeding 18 g. %; of these, one died of a ruptured spleen and two had splenomegaly; the fourth had a terminal gastrointestinal hemorrhage. Of those with hepatomas, 88% had an elevated sedimentation rate and 70% showed proteinuria.

In primary carcinoma of the liver, the two most commonly reported biochemical abnormalities are a high alkaline phosphatase and an elevated $alpha_2$ globulin.[11] In our series, the alkaline phosphatase was greater than 13 King-Armstrong units in 78%. Hyperglobulinemia was observed in 42% and hypoalbuminemia in 75%. Unfortunately, electrophoretic analysis was not done.

Other liver function tests showed varying degrees of abnormality (Table VIII).

It has been emphasized that a high right diaphragm is helpful in diagnosing primary liver cancer. This was described in seven of 24 patients who had chest radiographs. Of 44 barium studies of the gastrointestinal tract, 12 showed displacement of the stomach, duodenum and colon by a mass in the right upper quadrant, and two showed displacement of the right kidney. Hepatomegaly was demonstrated in four patients and splenomegaly in two. Fourteen of 16 cholecystograms were abnormal; 11 showed non-functioning gallbladders and two showed calculi.

In the 96 patients in the present study, the immediate causes of death were determined in 86 for whom adequate clinical and autopsy information was available. The results are summarized in Table IX. In 28 patients death was the result of hepatic failure; 11 were frankly comatose terminally. Seventeen had a terminal episode of gastrointestinal bleeding, and, in addition to the 11 noted above, six of these had hepatic coma. Pneumonia and carcinomatosis were less frequent causes of death. Death was due to intraperitoneal hemorrhage in two cases. Miscellaneous causes of death included heart failure, cerebrovascular accidents and pulmonary emboli. There were two postoperative deaths.

TABLE IX.—CAUSES OF DEATH IN 86 PRIMARY LIVER CARCINOMAS

| | *No.* | *Per cent* |
|---|---|---|
| Hepatic failure | 28 | 33 |
| Gastrointestinal hemorrhage | 17 | 20 |
| Pneumonia | 16 | 19 |
| Carcinomatosis | 13 | 15 |
| Hemoperitoneum | 2 | 2 |
| Miscellaneous | 10 | 12 |

In 77 patients for whom the date of onset of symptoms could be fixed with a reasonable degree of accuracy, the average duration of symptoms until death was less than six months in 65%, six to 12 months in 19%, and greater than 12 months in 16%. The shortest period was seven days and the longest interval of continuing symptoms was three and one-half years.

## DISCUSSION

Until recently the attitude of therapeutic nihilism associated with primary hepatic carcinoma made its diagnosis largely an academic exercise. Similarly, because of its alleged rarity, this tumour has frequently been excluded from differential diagnoses even though, with an overall autopsy rate of 0.29%, it is one-half as frequent as carcinoma of the gallbladder and one-third as frequent as carcinoma of the pancreas.

Active peptic ulceration is a frequent finding in cirrhotic subjects. Lipp and Lipsitz[12] give a figure of 19% and Elkington, McBrien and Spencer[11] of 14%. These authors find that the association is even stronger when the cirrhosis is complicated by a hepatoma; peptic ulceration then occurs in 23% of cases. In the present series 15 patients had a peptic ulcer. As Elkington points out, the association between primary hepatic malignancy and peptic ulcer may have important clinical implications, since further investigation of upper abdominal pain in cirrhosis may be abandoned when an ulcer is demonstrated unless it is appreciated that cirrhosis, hepatoma and an ulcer may co-exist.

Although stones in the intrahepatic ducts have been cited as an etiological factor in cholangioma,[16] no association was found in this series. However, 22 (almost one-quarter) of the patients had gallstones. This finding is frequent in hepatoma, and we agree with Overton, Kaden and Levisay[13] that evidence of biliary tract disease in jaundiced patients does not exclude hepatoma, because gallbladder function in 14 of 16 patients in this series who had cholecystograms was poor or absent.

The occurrence of diabetes mellitus in three out of 96 patients is within normal limits. Four cases of malignancy superimposed on hemochromatosis in this series is to be expected. Another interesting feature in this series was the co-existence of three proved independent malignant tumours—a squamous carcinoma of the lower lip, a meningioma and an adenocarcinoma of the stomach.

In general, the clinical features in the present survey are similar to those reported in other series, and attention has been directed only to those features that differ from other reports or were outstanding in this survey.

In view of the relatively low incidence of cirrhosis (38.5%) in the present series, the high frequency of bleeding complications (27%) is especially significant. Seventeen of 26 patients with gastrointestinal bleeding died of massive hemorrhage, the second most frequent cause of death. Intraperitoneal hemorrhage from rupture of the liver capsule occurred in one case—a finding reported by Berman[14] and others.[2, 9, 15] Rupture of the spleen with intraperitoneal exsanguination occurred in one case. This patient had polycythemia vera.

An abdominal mass was a more frequent complaint than in other series.[5, 7]

Pleural effusion was noted in almost one-quarter of the patients; one-third of these had pulmonary metastases and one-quarter were cirrhotic. The frequent occurrence of pleural effusions in this series is remarkable because of its virtual absence in other reported series. One would expect it to be a not uncommon finding in view of the relatively high incidence of decompensated cirrhosis in other reports.

Fever has frequently been stressed as a feature in the advanced stage of hepatoma.[4, 6, 9, 14, 15] It was a rare finding in this series.

Unusual manifestations of hepatoma in this series were the Budd-Chiari syndrome in one case and polycythemia in four.

According to San Jose *et al.*,[15] "The pattern of high alkaline phosphatase values and the absence of jaundice in patients without bone disease is a valuable clue to 'space-occupying lesions', including primary and metastatic carcinoma of the liver." We agree. Overton, Kaden and Levisay[13] report that in jaundiced patients the elevation in the alkaline phosphatase is disproportionate to that expected on the basis of the bilirubin level. We did not note this disparity in our series but agree that this would be of considerable diagnostic significance if present.

The serum proteins were altered in a large percentage of the patients tested. Though lacking diagnostic specificity, these and the other liver function tests afforded valuable evidence of serious hepatic disease. The results of routine laboratory tests contributed little to the diagnosis except for the consistent elevation of the sedimentation rate.

It is interesting to note that 70% of the patients had proteinuria. The significance of this finding is not completely understood. Five of these patients had known renal disease. Twenty-five of 33 patients with hypoalbuminemia had proteinuria. It would have been interesting to obtain urine electrophoretic patterns to determine the nature of this protein.

Schatzki[18] has discussed the radiographic criteria for the diagnosis of primary carcinoma of the liver. Despite radiological evidence consistent with these criteria in the present series, their signficance was not appreciated at the time and, for this reason, routine radiologic methods did not contribute significantly to the diagnosis.

The causes of death and the duration of symptoms agree with those reported in the literature. The ominous nature of primary liver cancer is apparent from the fact that two-thirds of the patients were dead six months after the diagnosis was made.

## SUMMARY

A review of 96 cases of primary carcinoma of the liver in Alberta during 1949-1965 is presented, and the findings in this and other reported series are compared. Primary cancer of the liver in Alberta has the following features: Cirrhosis was a predisposing cause in relatively few cases. The disease may occur at any age, but it is most common in the seventh and eighth decades. Males predominantly are affected. Hepatomas are three times as common as cholangiomas. Associated disorders, including peptic ulcers and cholelithiasis, are not uncommon. The most common clinical features are hepatomegaly, abdominal pain, weight loss and ascites. Attention is drawn to the features of this condition since only by early diagnosis may surgery offer a possible cure to an otherwise invariably fatal disease.

## REFERENCES

1. STRONG, G. F., PITTS, H. H. AND MCPHEE, J. G.: *Ann. Intern. Med.*, **30**: 791, 1949.
2. WILBUR, D. L., WOOD, D. A. AND WILLETT, F. M.: *Ibid.*, **20**: 453, 1944.
3. GREENE, J. M.: *Surg. Gynec. Obstet.*, **69**: 231, 1939.
4. GUSTAFSON, E. G.: *Ann. Intern. Med.*, **11**: 889, 1937.
5. SANFORD, C. H.: *Ibid.*, **37**: 304, 1952.
6. SPATT, S. D. AND GRAYZEL, D. M.: *Amer. J. Med.*, **5**: 570, 1948.
7. EDMONDSON, H. A. AND STEINER, P. E.: *Cancer*, **7**: 462, 1954.
8. ANDERSON, W. A. D., editor: Pathology, 2nd ed., The C. V. Mosby Company, St. Louis, 1953, p. 858.
9. MACDONALD, R. A.: *A.M.A. Arch. Intern. Med.*, **99**: 266, 1957.
10. BENNER, E. J. AND LABBY, D. H.: *Ann. Intern. Med.*, **54**: 620, 1961.
11. ELKINGTON, S. G., MCBRIEN, D. J. AND SPENCER, H.: *Brit. Med. J.*, **2**: 1501, 1963.
12. LIPP, W. F. AND LIPSITZ, M. H.: *Gastroenterology*, **22**: 181, 1952.
13. OVERTON, R. C., KADEN, V. G. AND LEVISAY, W. R.: *Surgery*, **37**: 519, 1955.
14. BERMAN, C.: Primary carcinoma of the liver, H. K. Lewis & Co. Ltd., London, 1951.
15. SAN JOSE, D. *et al.*: *Amer. J. Dig. Dis.*, **10**: 657, 1965.
16. SANES, S. AND MACCALLUM, J. D.: *Amer. J. Path.*, 18: 675, 1942.
17. SCHUPBACH, H. J., JR. AND CHAPPELL, R. B.: *A.M.A. Arch. Intern. Med.*, **89**: 436, 1952.
18. SCHATZKI, R.: *Amer. J. Roentgen.*, **46**: 476, 1941.
19. SHELDON, W. H. AND JAMES, D. F.: *Arch. Intern. Med. (Chicago)*, **81**: 666, 1948.
20. HIGGINSON, J.: *Brit. J. Cancer*, **10**: 609, 1956.
21. GALL, E. A.: *A.M.A. Arch. Path.*, **70**: 226, 1960.